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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/584,072
Filing Date: April 03, 2007
Appellant(s): ANSORGE ET AL.

Sagun KC
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 02/04/2010 appealing from the Office action mailed 06/11/2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:1-3, 5-8 and 10-15.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

20040167153	YEADON et al.	8-2004

Biewenga et al. "Lipoic Acid Favor's Thiolsulfinate Formation after Hypochlorous Acid Scavenging: A Study with Lipoic Acid Derivatives" Arch. Biochem. Biophys., vol. 312, no. 1 (March 9, 1994), pp.114-120

MIRA et al. " Scavenging of Reactive Oxygen Species by Silibinin Dehemisuccinate" Biochemical Pharmacology, vol. 48 (1994), no. 4, pp. 753-759.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-3, 5-8 and 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biewenga et al. (Arch. Biochem. Biophys. (1994);312(1):114-20) in view of Mira et al. (Biochem. Pharmacol. (1994);48(4):753-9), the combination further taken in view of US 2004/0167153 .

The primary reference discloses that hypochlorous acid (HOCL) is an oxidant that has a prominent effect in inactivation or alpha-1-anti-proteinase. Due to this inactivation, the ability of the anti-proteinase to inhibit elastase is lost. The resulting higher activity of elastase is held responsible for tissue damage in lung emphysema. It further discloses that lipoic acid possesses HOCL-scavenging activity. *See abstract.* The reference does not expressly teach silibinin or inhalation.

The secondary reference discloses that silibinin dihemisuccinate (SDH) is also an HOCL scavenger. It additionally discloses that a compound that is a good HOCL scavenger of HOCL will protect alpha-1-anti-proteinase against inactivation by HOCL

over the concentration range present *in vivo*. The reference further discloses that even micromolar concentrations of SDH in buffer solution were able to protect alpha-1-anti-proteinase from HOCL. It is known that when SDH is administered in a dose of 5 mg/kg, a concentration of 50 micrograms/mL (68.8 micromolars) is reached at the end of a 2-hr infusion. Thus, SDH may scavenge HOCL at a rate fast enough to protect important targets *in vivo*, such as alpha-1-anti-proteinase. *See pg, 758, 1st full para.* The results presented in the reference, when combined with the knowledge that silibinin has low toxicity, support a potential role for silibinin as an antioxidant drug. *See page 758, last full sentence in 1st column.* The reference does not expressly teach lipoic acid or inhalation.

The tertiary reference discloses combination therapy using aerosol or dry powder formulations [0110] for simultaneous, sequential or separate administration by the inhaled route in the treatment of obstructive airways or other inflammatory disease, such as asthma or emphysema [0065] (abstract). The reference does not expressly teach alpha-lipoic acid or silibinin.

It would have been obvious at the time of the invention to one of ordinary skill in the art to protect damage to lung cells of chronically obstructed lungs, such as emphysemic lungs, by administering a composition through inhalation, wherein the composition consists of silibinin, alpha-lipoic acid and a pharmaceutically acceptable carrier. The skilled artisan would have been motivated to combine silibinin with alpha-lipoic acid by the desire to use the HOCL scavenging qualities of both compounds to prevent HOCL from ultimately increasing the tissue damaging properties of elastase

since this elastase activity is considered responsible for lung damage in emphysema. The artisan would also have a reasonable expectation to, at least, render an additive scavenger effect against HOCL by using these compounds together in combinatory therapy. Generally, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose; the idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980): In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960). Conversely, there is no evidence in the record establishing the Appellant's combination of agents is any more effective or in any way different than any single member of that combination. See In re Dial, 140 USPQ 244 (C.C.P.A. 1964). In this case, both alpha-lipoic acid and silibinin are known as effective HOCL scavengers that would protect anti-1-proteinase from inactivation.

As for the claimed dosages, it is known in the art of pharmaceutical therapy that drug dosages can be calculated and adjusted depending on many different factors, such as, inter alia, weight, sex, age, frequency of administration, the form of the medication and channel of administration. Generally, it is not patentable to optimize the concentration of ingredients in a composition through routine experimentation. Differences in concentration from what is disclosed in the reference, will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. It is not inventive to discover the optimum or workable ranges by routine experimentation. *See MPEP 2144.05 [R-5] II A*. Accordingly,

varying dosage amounts is an obvious step in the treatment of subjects who vary in weight or age, for example.

(10) Response to Argument

Appellant argues that the examiner's reliance on *In re Kerkhoven* is misplaced because the compounds of each reference are not taught to be useful for the same specific purpose. As such appellant concludes that the rejection should be withdrawn. The examiner disagrees. As an initial matter, the examiner notes that there are 2 rationales provided in the rejection for the reasons why one of ordinary skill in the art would have combined lipoic acid with silibinin to treat COPD:

> 1) "The skilled artisan would have been motivated to combine silibinin with alpha-lipoic acid by the desire to use the HOCL scavenging qualities of both compounds to prevent HOCL from ultimately increasing the tissue damaging properties of elastase since this elastase activity is considered responsible for lung damage in emphysema. The artisan would also have a reasonable expectation to, at least, render an additive scavenger effect against HOCL by using these compounds together in combinatory therapy", and
>
> 2) "Generally, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose; the idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980): In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960). Conversely, there is no evidence in the record establishing the Applicant's combination of agents is any more effective or in any way different than any single member of that combination. See In re Dial, 140 USPQ 244 (C.C.P.A. 1964). In this case, both alpha-lipoic acid and silibinin are known as effective HOCL scavengers that would protect anti-1-proteinase from inactivation".

The examiner further notes that appellant has not provided any reason why the first rationale does not support a *prima facie* case of obviousness. For this reason alone, the appellant's arguments that a *prima facie* case of obviousness has not been made should be found unpersuasive. Regarding appellant's arguments that the reliance on *in re Kerkhoven* is misplaced because the compounds of each reference are

not taught to be useful for the same specific purpose, the examiner does not find this argument persuasive because the references clearly are directed to the HOCl antioxidative scavenging effects of silibinin (Mira reference; title; abstract and throughout) and lipoic acid (Biewenga reference; title and throughout). The disclosures of the HOCl scavenging effects of each agent provides the motivation to one of ordinary skill of reasonable expectation to have at least an additive HOCl scavenging effect when the agents are combined together. Since HOCl exacerbates the problem with increased elastase and emphysema, then it would be reasonable to use agents taught to decrease the effect of HOCl for the treatment of emphysema.

As for the unexpected results, appellant refers to data exemplified in Example 4 (Table 6) and Example 5 (Table 7) which allegedly shows that the combination of silibinin with lipoic acid leads to unexpected results compared to the COPD control. The examiner does not find any unexpected results in the data presented in these examples.

First, it is noted that the data in Tables 6 and 7 do not necessarily show an additive effect, much less a superadditive effect when silibinin and lipoic acid are combined to treat COPD relative to the COPD control. When the wide degrees of deviations disclosed in the tables are considered, it appears that the data show about the same thiol concentration as the control for COPD. For example, Table 6 discloses that, 24 hours after the administration of 10 micrograms/ml lipoic acid and 70 micrograms/ml silibinin, a concentration value of 102 +/- 22.6 (i.e., 79.4 to 124.5) is demonstrated. The concentration value for the COPD control is 61.6 +/- 13.9 (i.e., 47.7 to 79.9). When the upper end of the control (I.E., 79.9) is compared to the lower end of

the test (I.E., 79.4), the thiol concentrations are about the same. Table 7 shows a similar pattern in the effect on macrophage phagocytosis. Accordingly, the data cannot be considered to show any superadditive effect.

Second, both silibinin and lipoic acid are both used for the same purpose in the examples, i.e., to increase cellular thiol expression and inducing phagocytosis. Appellant claims to have data that shows that a combination of 70 micrograms silibinin with 10 micrograms of lipoic acid demonstrates an unexpected increase in thiol expression and phagocytosis. However, appellant has compared these results to those obtained when either using 70 micrograms silibinin alone or using 10 micrograms lipoic acid alone. Since the total amount of agent used to show alleged unexpected results was 80 micrograms (i.e., 70 +10 micrograms), it would appear that a proper showing of unexpected results would also include a comparison to 80 micrograms of lipoic acid alone and 80 micrograms of silibinin alone. Appellant has not provided data showing this comparison; therefore, the showing is not considered to be a proper showing of unexpected results.

The examiner contends that, even if unexpected results were demonstrated, *in arguendo,* the claims are not commensurate in scope to any example in Tables 6 or 7. Appellant argues, however, that insofar as the objective indicia of unobviousness for the claimed combination has been established by the way of experimental evidence, and the examiner has failed to provide any reasons as to why one of ordinary skill in the art would doubt that doses that are different from the exemplified doses would cease to yield the demonstrated pharmacological effects. Examiner disagrees. The showing of

unexpected results must be reviewed to see if the results occur over the entire claimed range. MPEP 716.02(d)R2. Appellant indicates that the mere combination of silibinin, at any concentration, with lipoic acid, at any concentration, would lead to a superadditive increase in cellular thiol expression and macrophage phogocytosis. This indication is not supported by the data in Tables 6 or 7. For example, in the last row of Table 6, 10 micrograms/ml of lipoic acid in combination with 700 micrograms/ml of silibinin showed a *lower* concentration of cellular thiol expression relative to the control COPD data. This alone is clear evidence that merely combining lipoic acid and silibinin does not lead to a superadditive effect as alleged. Accordingly, the claims would have to be further limited to be commensurate in scope with any objective data alleging to show unexpected results as required by MPEP 716.02(d)R2.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/C. E. S./

Examiner, Art Unit 1612

Conferees:

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612

/Michael Hartley/

Supervisory Patent Examiner, Art Unit 1618